

REMARKS

A. Status of the Claims

Claims 17-33 were examined in the Action. Claims 17 and 25 have been amended. Support for these amendments can be found in the specification and claims as originally filed. *See, e.g.*, p. 6, third full paragraph; p. 7, first full paragraph; p. 17, third full paragraph; and originally-filed claim 17. No new matter has been added.

B. Amendments to the Specification

The specification has been amended to correct typographical errors at pages 18-19 and 21.

C. Claim Objection

Claim 17 is objected to because of a lack of clarity regarding which molecules are truncated. Applicants have amended claim 17 to clarify that it is a “cDNA molecule” that is truncated at least 30 nucleotides downstream of the start codon and truncated at least 30 nucleotides upstream of the stop codon of the full length tau cDNA sequence coding for 4-repeat and 3-repeat tau protein.

In addition, to further clarify which molecules are truncated, reference to GenBank Accession Number NM_173727 was deleted from claim 17. Applicants recently accessed the GenBank database and discovered that when one looks up NM_173727, a message stating that “The record has been replaced by NM_005910” is displayed. For the Examiner’s convenience, a print out of this screen is attached as Appendix 1. Thus, the sequence referenced in the present specification is now available under Accession Number NM_005910. To avoid confusion in the current claims, reference to GenBank Accession Number NM_173727 was deleted. The relevant part of claim 17 now recites: “the cDNA molecule has truncated at least 30 nucleotides

downstream of the start codon and truncated at least the 30 nucleotides upstream of the stop codon of the full length tau cDNA sequence coding for 4-repeat and 3-repeat tau protein....” As described in the first paragraph on page 7 of the present specification, the full length tau cDNA sequence coding for 4-repeat and 3-repeat tau protein is disclosed in Goedert *et al.*, *Neuron*, 3:519:526 (1989). Accordingly, in view of the disclosure in the present specification, a person of ordinary skill in the art will be able to understand which sequence is being referred to by the recitation “the full length tau cDNA sequence coding for 4-repeat and 3-repeat tau protein.”

In view of the above, Applicants respectfully request reconsideration and the withdrawal of this objection.

D. The Rejections Under 35 U.S.C. § 112, First Paragraph Are Overcome

Claim 17 is rejected under 35 U.S.C. § 112, first paragraph, as indefinite in its recitation of “the minimally truncated tau core.” Applicants generally traverse this rejection, but have amended claim 17 to read, in pertinent part, “...the cDNA molecule comprising SEQ ID No. 9....”

Claims 25-27 are rejected as being incomplete for omitting essential steps. In particular, the Action states that the claims omit the step of the administration and evaluation of a candidate to a transgenic non-human animal of claim 17. The Action, p. 3. Current claim 25, from which claims 26 and 27 depend, recites the step of “administering the candidate to a non-human transgenic animal of claim 17.”

Applicants respectfully request reconsideration and withdrawal of the indefiniteness rejections.

E. The Rejection Under 35 U.S.C. § 112, First Paragraph, Is Overcome

Claims 17-33 are rejected under 35 U.S.C. § 112, first paragraph, as failing to comply with the enablement requirement. Specifically, the Action asserts that there is insufficient description of the DNA construct used to produce the transgenic rat disclosed in the specification to establish that the DNA construct is encompassed by claim 17; that there is no correlation shown between the expression of the transgenic tau protein in rat with any useful phenotype; and that the specification fails to teach how to make and use any transgenic animals other than rats. Applicants traverse this rejection.

1. Claim 17 Is Enabled

The specification discloses 14 specific cDNA sequences encompassed by claim 17 that can be used to generate transgenic rats. *See, e.g.*, pp 6-15; and Figs 1-6, described at pp 18-20. A specific example of a transgenic animal encompassed by claim 17 is transgenic rat #318 described in the working examples in the present specification. To provide additional evidence of the enablement of the claimed invention, Applicants submit as Appendix 2 the declaration of Peter Filipcik ("Filipcik Declaration"). Dr. Filipcik is an inventor of the present application and a co-author of the publication Zilka *et al.*, *FEBS Letters* 580:3582-3588 (2006) ("the Zilka reference").

The Zilka reference describes the generation and analysis of transgenic rat lines #318 and #72. The transgene construct used in the generation of transgenic rat lines #318 and #72 described in the Zilka reference was prepared by ligation of a cDNA coding for human tau protein truncated at amino acid positions 151-391 into the mouse Thy-1 gene downstream of the brain promoter/enhancer sequence (Filipcik Declaration, para. 6). Transgenic rat line #318 in the Zilka reference is the same rat line described in the present specification (Filipcik Declaration,

para. 6). It should be noted, however, that the numbering of the amino acids of the tau protein in the Zilka reference is based on tau isoform 40, whereas the numbering in the present patent application is based on tau isoform 43 (Filipcik Declaration, para. 6). Tau isoform 40 contains an extra insert of 58 amino acids (174 nucleotides) in the N-terminus of the protein (Filipcik Declaration, para. 6). Thus, the truncated tau protein numbered amino acids 151-391 in the Zilka reference is the same as a truncated tau protein numbered amino acids 93-333 based on the numbering in the present specification (Filipcik Declaration, para. 6). Using the numbering in the patent application, amino acids 93-333 correspond to nucleotides 279-999 (Filipcik Declaration, para. 6). Thus, the truncated tau cDNA molecule used to generate rat line #318 is truncated at least 30 nucleotides downstream of the start codon and truncated at least the 30 nucleotides upstream of the stop codon of the full-length tau cDNA sequence coding for 4-repeat and 3-repeat tau protein; and the truncated tau cDNA molecule comprises SEQ ID NO: 9 (nucleotides 741-930) (Filipcik Declaration, para. 6). *See also Specification, Fig. 1.*

Furthermore, transgenic rat line #318 is described in the specification as exhibiting neurofibrillary pathology producing activity when expressed in brain cells of this rat line. *See, e.g., Figs. 6-8 and 10 and their accompanying descriptions at pp 19-21 and 25, and Example 5 at pp 24-25 of the specification.* This is further supported by studies reported in the Zilka reference (Filipcik Declaration, para. 9).

The evidence above demonstrates that transgenic rat line #318 comprises a DNA construct comprising a cDNA molecule coding for N- and C-terminally truncated tau molecules, wherein: (1) the cDNA molecule is truncated at least 30 nucleotides downstream of the start codon and truncated at least the 30 nucleotides upstream of the stop codon of the full-length tau cDNA sequence coding for 4-repeat and 3-repeat tau protein; (2) the cDNA molecule comprises

SEQ ID No. 9; and (3) the DNA construct encodes a protein, which has neurofibrillary (NF) pathology producing activity when expressed in brain cells.

2. Transgenic Tau Proteins of the Present Invention Are Associated With Useful Phenotypes

The Action states that there is no correlation shown between the expression of the transgenic tau protein in rat with any useful phenotype. The Action, pp 9-10. However, Fig. 10 and the accompanying descriptions on pages 20-21 and 25 of the specification depict a comparison of neurofibrillary pathology in the brains of patients suffering from Alzheimer's disease and those observed in the brain of transgenic rat line #318. Equivalent pathological structures were observed when comparing the two samples. *Id.* See also Figs. 6-8 and their accompanying descriptions at pp 19-20. These results demonstrate a useful phenotype in the transgenic animal.

The association of the truncated tau protein with the phenotype of neurofibrillary pathology was also studied in the Zilka reference. As stated on p. 3585 of the Zilka reference,

3.5. The level of sarcosyl insoluble formation correlates with lifespan of transgenic rats expressing truncated tau

Sarcosyl insolubility of tau is generally considered to be a definitive transformation point of physiological tau into pathological form. Therefore, we analysed development of sarcosyl insoluble tau complexes in the brain of transgenic rats expressing truncated tau (1151-391). The brain tissues were examined at 3, 6, 9 and 12 months old animals. The level of tau in the sarcosyl insoluble P2 fraction increased in an age-dependent manner and correlated positively with the development of neurofibrillary pathology. First sarcosyl

Therefore, the Zilka reference also confirms the association of the expression of truncated tau protein as encoded by a cDNA of the present invention with useful phenotypes.

Moreover, Exhibit 3 of the Filipeik Declaration describes additional phenotype experiments performed with transgenic rat line #318. The Filipeik Declaration confirms that the

phenotypes observed in these experiments—cognitive impairment, oxidative stress, metabolic (energy) stress, and phosphorylation—qualify transgenic rat line #318 as a suitable model for Alzheimer’s disease (Filipcik Declaration, para. 11 and 12).

Furthermore, in addition to the transgenic rat lines #318 and #72, which were generated in the SHR genetic background, the same DNA construct was introduced into the Wistar rat genetic background (Filipcik Declaration, para. 13). The transgenic rat line in the Wistar background exhibited the same neurofibrillary pathology phenotype as the transgenic rat lines in the SHR background (Filipcik Declaration, para. 13). This result indicates that the observed phenotype is associated with the expression of the truncated tau protein and not with the genetics of any particular rat line (Filipcik Declaration, para. 13).

3. The Specification Is Enabling for Making and Using Transgenic Animals Other Than Rats

The Examiner has the initial burden of producing reasons that substantiate a rejection based on lack of enablement. *In re Marzocchi*, 439 F.2d 220, 224, 169 USPQ 367, 370 (CCPA 1971). This burden requires a factual basis or scientific principle to reasonably doubt the accuracy of a clear disclosure to be supplied. *Id.* The Action, however, failed to provide a factual basis or scientific principle to reasonably doubt the accuracy of the present disclosure.

The Action asserts that the specification fails to provide sufficient guidance to one of ordinary skill in the art how to make and use transgenic animals other than rats in accordance with the present claims without undue experimentation. The Action supports this assertion in part by citing to several journal articles that discuss individual differences between species leading to different expressions and unpredictable results. However, these cited publications do not relate to or discuss the expression of tau protein as described in the present invention, and cannot support the enablement rejection.

More specifically, the publications relate to the generation of knock-out mice (Williams *et al.*, 2000), microinjection methods of different organisms (Hammer *et al.*, 1986), different physiological backgrounds in the expression of human major histocompatibility complex in mice (Hammer *et al.*, 1990), variation of the tumor formation time and size after knock-out of p53 tumor suppressor gene (Sigmund *et al.*, 2000), organ transplantation problems (Loga *et al.*, 1999), the complexity of protein structure prediction using *in silico* methods (Ngo *et al.*, 1994), the characteristics endowed on protein hormones by the constituent amino acids (Parsons *et al.*, 1976) and a discussion of retrovirus vectors for transfecting birds (Shuman *et al.*, 1991). None of these references discuss the expression of tau proteins as described in the present application, and are instead drawn toward general aspects of transgenic science or descriptions of transgenic models of specific diseases that are unrelated to Alzheimer's disease. Applicants also note that several of these publications are over 15 years old: relative to the rapid evolution in each of these technologies, these publications are arguably outdated and do not strongly support a nonenablement rejection.

The MPEP states that "the test for enablement is whether one reasonably skilled in the art could make or use the invention from the disclosures in the patent coupled with information known in the art without undue experimentation." MPEP § 2164.01 (*quoting United States v. Electronics, Inc.*, 8 USPQ2d 1217, 1223 (Fed. Cir. 1988)).

It is well known in the art of transgenic science that there are examples wherein the expression of identical or homologous gene constructs in different animals results in those animals exhibiting similar phenotypes. *See, e.g.*, Gurney *et al.*, *Science* 264:1772-74 (1994) and Howland *et al.*, *PNAS* 99:1604-09 (2002) (transgenic expression of the same mutated superoxide dismutase in mice and in rats resulted in nearly the same phenotype); von Horsten *et al.*, *Human*

Mol. Gen. 12:617-24 (2003); Bates *et al.*, *Human Mol. Gen.* 6:1633-37 (1997); Mangiarini *et al.*, *Cell* 87:493-506 (1996) (animal modeling of Huntington's disease in mice and rats found to be comparable) (Exhibits 4-8, respectively). In view of the studies discussed above, it is reasonable to conclude that expression of cDNAs of the present invention in animals other than rats, such as mice, would be enabled by the specification and knowledge available to one of ordinary skill in the art (Filipcik Declaration, para. 14).

Furthermore, as discussed in the Filipcik Declaration, similarities exist between rats and mice such that it is likely that the phenotype(s) observed in transgenic rats using cDNAs of the present invention will be observed in mice (Filipcik Declaration, para. 14). These similarities are also discussed in the literature. *See, e.g.*, Exhibit 8 (Rat Genome Sequencing Project Consortium, *Nature* 428:493-521 (2004), particularly Fig. 7). These observations further indicate that the claims are enabled by the specification in combination with knowledge available to those of skill in the art at the time the present application was filed.

4. Summary

As long as the specification discloses at least one method for making and using the claimed invention that bears a reasonable correlation to the entire scope of the claim, then the enablement requirement of 35 U.S.C. § 112 is satisfied. *In re Fisher*, 427 F.2d 833, 839, 166 USPQ 18, 24 (CCPA 1970). As described above, the specification teaches a specific method for making and using a non-human transgenic animal encompassed by the claims.

Furthermore, in view of the considerable guidance provided in the specification concerning the preparation of DNA constructs and the creation of transgenic animals, a person of ordinary skill in the art would be able to practice the claimed invention without undue experimentation. Even if experiments are necessary, a considerable amount of routine experimentation is permissible, especially where the specification provides a reasonable amount

of guidance with respect to the direction in which experimentation should proceed. *Ex parte Forman*, 230 USPQ 546, 547 (Bd. Pat. App. & Int. 1986). Such guidance has been provided in the specification. For example, the specification teaches the preparation of constructs of the present invention and their injection into male pronuclei of one-day old rat embryos via microinjection. *See, e.g.*, p. 12, first full paragraph; p. 13, third full paragraph; Examples 1-2 at pp 21-22 and accompanying Figs. 1-2, described at p. 18. Genotyping of animals born after embryo implantation and assessment of the transmission of the injected construct is described in the specification at, for example, pp 13-14; Example 3 at pp 22-23 and accompanying Fig. 3, described at pp 18-19. Confirmation of the presence of proteins encoded by cDNAs of the present invention in rat brains is also described. *See, e.g.*, pp 14-15; Figs. 4-5 and their accompanying descriptions at p. 19; and Example 4 at pp 23-24. Experiments assessing phenotypes associated with truncated tau proteins of the present invention are also presented. *See, e.g.*, p. 15, second and third full paragraphs; Figs. 6-8 and 10 and their accompanying descriptions at pp 19-21 and 25; and Example 5 at pp 24-25. Screening assays for drug leads and candidates are also described. *See, e.g.*, pp 16-18; Fig. 9 and its accompanying description at p. 20; and Example 6 at pp 25-26.

Because no undue experimentation is required to make and use the present invention in light of the guidance provided in the specification and knowledge available to one of ordinary skill in the art, the enablement rejection cannot stand and Applicants respectfully request its withdrawal.

The Examiner is invited to contact the undersigned attorney with any questions, comments or suggestions relating to the referenced patent application.

Respectfully submitted,



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